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<u>L43</u>	L42 and l39	52	<u>L43</u>
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<u>L41</u>	solvent with remov\$	221261	<u>L41</u>
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<u>L36</u>	l31 or polynucleotide	204615	<u>L36</u>

<u>L35</u>	L34 with l29	11	<u>L35</u>
<u>L34</u>	emulsion or organic solvent	597475	<u>L34</u>
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<u>L31</u>	dna or nucleic or plasmid or polynucleotide	197219	<u>L31</u>
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<u>L3</u>	micelle	13812	<u>L3</u>
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File: PGPB

Apr 4, 2002

DOCUMENT-IDENTIFIER: US 20020039596 A1

TITLE: PRODUCTION OF MULTIVESICULAR LIPOSOMES

Summary of Invention Paragraph (18):

[0017] In one aspect, the invention provides a process for producing MVL by providing a water in oil (w/o) emulsion, which is made from an aqueous phase dispersed in a solvent phase containing amphipathic and neutral lipids. Amphipathic lipids can be chosen from a large group including phosphatidylcholines, phosphatidylethanolamines, sphingomyelins, lysophosphatidylcholines, lysophosphatidylethanolamines, are phosphatidylglycerols, phosphatidylserines, phosphatidylinositols, phosphatidic acids, cardiolipins, acyl trimethylammonium propane, diacyl dimethylammonium propane, stearylamine, and ethyl phosphatidylcholine. Neutral lipids can be selected from glycerol esters, glycol esters, tocopherol esters, sterol esters, alkanes and squalenes. Physiologically active substances can be included in either the aqueous or solvent phase, and are chosen from a wide range of materials including antianginas, antiarrhythmics, antiasthmatic agents, antibiotics, antidiabetics, antifungals, antihistamines, antihypertensives, antiparasitics, antineoplastics, antitumor drugs, antivirals, cardiac glycosides, hormones, immunomodulators, monoclonal antibodies, neurotransmitters, nucleic acids, proteins, radio contrast agents, radionuclides, sedatives, analgesics, steroids, tranquilizers, vaccines, vasopressors, anesthetics, peptides, prodrugs and pharmaceutically acceptable salts of these materials. Specific materials such as cytarabine, insulin, paclitaxel, 5-fluorouracil, floxuridine, morphine, hydromorphone, dexamethasone, methotrexate, bleomycin, vincristine, vinblastine, IgF-1, bupivacaine and amikacin can be included.

Detail Description Paragraph (11):

[0069] In the practice of the invention, the first emulsion is formed by high-shear mixing of two immiscible solutions. In general, one solution comprises liposome-forming lipids and/or oils dissolved in a water-immiscible solvent (which could be an organic solvent), and the other solution comprises a first aqueous formulation. A physiologically active compound is often added to at least one of the solutions, most typically at least the first aqueous phase. The first aqueous phase often also includes pH buffering agents, osmotic agents, release-modifying compounds, and the like. There can also be acids of various types included in the first aqueous phase, as detailed in copending U.S. patent application Ser. No. 08/792,566. The water-immiscible solvent phase can also contain biodegradable polymers or copolymers, as detailed in copending U.S. patent application Ser. No. 60/101,855 hereby incorporated by reference. The first emulsion is mixed by mechanical means, ultrasound, nozzle atomization, or the like, until the desired droplet size is reached. Static mixing (to be described in detail below) can also be employed at this stage, to make the first w/o emulsion.

Detail Description Paragraph (16):

[0074] The first emulsion can contain a number of useful substances, including flavoring or fragrant components, cosmetic products, waste materials, or pharmaceutical materials, including physiologically active materials. These substances can be introduced into either the aqueous or solvent phases. In certain preferred embodiments, the first emulsion can contain at least one physiologically active substance. This produces pharmaceutical compositions comprising MVL. Physiologically active substances are those natural, synthetic or genetically engineered chemical or biological compounds or entities that have utility for modulating physiological processes in order to afford diagnosis of, prophylaxis against, or treatment of an undesired condition in a living being. Physiologically active substances include drugs such as antianginas, antiarrhythmics, antiasthmatic agents, antibiotics, antidiabetics, antifungals, antihistamines, antihypertensives, antiparasitics, antineoplastics, antitumor drugs, antivirals, cardiac glycosides, hormones, immunomodulators, monoclonal antibodies,

neurotransmitters, nucleic acids, proteins, radio contrast agents, radionuclides, sedatives, analgesics, steroids, tranquilizers, vaccines, vasopressors, anesthetics, peptides and the like. Prodrugs which form the indicated physiologically active substances upon local interaction with the intracellular medium, cells, or tissues can also be employed in the invention. Any pharmaceutically acceptable salt of a particular physiologically active substance which is capable of forming such a salt is also envisioned as being useful in the present invention, including halide salts, phosphate salts, acetate salts, and other salts.

Detail Description Paragraph (85):

[0140] Viscosity measurements were measured using a capillary viscometer. The capillary viscometer is a silanized stainless steel tube (1.08 mm inside diameter, 50 cm in length, or 0.55 mm inside diameter, 50 cm in length; Alltech) attached to a pressure vessel and a digital pressure gauge and valve positioned at the entrance of the capillary tube. Flow from the tube was collected in a graduated cylinder. The viscometer was calibrated using Canon mineral oil standards with viscosities of 9.178 cP and 18.78 cP at 20.degree. C. The first emulsion vessels were held at 20.degree. C. during mixing unless temperature effects were being investigated. The temperature of the samples was recorded upon exit from the capillary tube. It did not vary more than +/-5.degree. with an average of 20.78.degree. C. and standard deviation of 0.85.degree. C. Second emulsion vessels were generally held at higher temperatures, for example 40.degree. C.

Detail Description Paragraph (137):

[0185] The flow rate of the first emulsion into a receiving vessel immediately before the static mixer was monitored by an in-line flow meter (Flow meter, EG&G, model #FT6-871W-LEGA1), and was controlled by a valve on the pressure vessel outlet. Flow rates are scale dependent and therefore not useful for scaling up. More useful are the linear velocities, which are determined by dividing the flow by the cross-sectional area of the particular static mixer used.

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L45: Entry 1 of 25

File: PGPB

May 15, 2003

DOCUMENT-IDENTIFIER: US 20030091649 A1

TITLE: ICAM-1 formulation having controlled-size microparticles

Abstract Paragraph (1):

Method and system of producing microparticles loaded with biologically active drugs, including proteins such as ICAM-1, for controlled release of the drugs in a nasal passageway. The method includes introducing a drug/polymer feed solution and an emulsifier into a first mixing chamber to create an emulsion, then mixing a cross-linking agent together with the emulsion under controlled conditions to create microparticles loaded with the drug. The system includes a first mixing chamber, in which the emulsion is created, having a first port for introducing the drug/polymer solution, and a second port angled substantially perpendicular to the first port for introducing the emulsifier. A second mixing chamber adjacent to the first mixing chamber receives the emulsion and either contains a cross-linking agent or receives a stream of a cross-linking agent to solidify the microparticles. The formed microparticles are filtered and deaggregated to form individual microparticles that then may be formulated for nasal passageway delivery.

Summary of Invention Paragraph (22):

[0019] The system of the invention comprises a semi-continuous flow system that mixes a drug-loaded, alginate stream, most preferably a low viscosity sodium alginate (LVCR), with an emulsifier stream to form an emulsion in a mixing chamber. At a point downstream either in the same or an adjacent mixing chamber, a stream containing a cross-linking agent, such as a calcium salt, is added to the emulsion. In the cross-linking process, sodium in the sodium alginate is replaced by calcium, forming a non-water soluble calcium alginate microparticles loaded with the drug. After collection, the microparticles are filtered, washed, dried in a vacuum oven and, if necessary, deaggregated using gentle pressure to produce individual drug-loaded microparticles that may be delivered via the nasal passageway.

Detail Description Paragraph (22):

[0050] Basically, a first port (104) lies along the horizontal axis of the block (100). A drug/polymer solution, discussed in further detail below, is introduced at a predetermined flow rate through first port (104) and into the first mixing chamber (102). A second port (106) is positioned essentially orthogonal to the interior wall of the first chamber (102) and off-set from the line of the stream flowing from the first port (104). An emulsifier is introduced at a predetermined flow rate through this port (106) and into the first mixing chamber (102) to form an emulsion with the drug/polymer solution within the first mixing chamber (102). In the illustrated embodiment of FIG. 4, both ports (408, 410) have the same inner diameter of 0.034 cm.

Detail Description Paragraph (44):

[0072] In practicing the present invention, a buffer solution may initially be passed through the port (104) into the first mixing chamber (102) prior to introduction of either the drug/polymer solution or the emulsifier to pre-fill the mixing chamber and to prime the pumps associated with the system. When both the solution and the emulsifier are simultaneously introduced into the first mixing chamber (102) via the two ports (104, 106), an emulsion is formed. The turbulence created within the first mixing block (102) by the countervailing streams of solutions entering the first mixing block (102) breaks up the minor liquid (i.e., the LVCR) into individual droplets. The size of the droplets depends on the amount of turbulence in the chamber and properties of both liquids, which is related to the Reynolds number of the system at the chamber. The higher the Reynolds number, the smaller the microparticle size. In addition, the more viscous the two solutions, the more difficult it is to create turbulence.

Detail Description Paragraph (45):

[0073] Once the microparticles are formed in the first mixing chamber (102), they flow into a second mixing chamber (108). The second mixing chamber (108) preferably is adjacent to the first mixing block (102), to facilitate flow of the emulsion containing the microparticles. In a preferred embodiment, the second mixing chamber (108) is contiguous with the first mixing chamber (102), as illustrated in FIG. 1.

Detail Description Paragraph (46):

[0074] If the second mixing chamber (108) is not contiguous with the first mixing chamber (102), then the emulsion may be transferred from the first mixing chamber (102) into an enlarged second mixing chamber that contains an amount of a cross-linking agent. In such embodiment, the cross-linking occurs essentially simultaneously, i.e., less than about 2 seconds; however, residence time in the chamber may extend from a few hours to a few days, depending on the microparticle composition and the cross-linking agent to further dehydrate the microparticles.

Detail Description Paragraph (62):

[0090] The flowchart of FIG. 3 outlines a preferred method of practicing the present invention. The drug/polymer solution is introduced (302) into the first mixing chamber (102) preferably simultaneously with the introduction (304) of the emulsifier into the first mixing chamber (102), thus forming (306) an emulsion containing the microparticles and solvent. The emulsion then is transferred (308) into the second mixing chamber (108), at which time the cross-linking agent is introduced (310) into the chamber (108).

## CLAIMS:

1. A system for forming microparticles loaded with a drug, comprising: A. a first mixing chamber, including: a first port for introducing a first stream of a first solution comprising a predetermined amount of said drug and microparticle-forming polymer into said first mixing chamber; and a second port for introducing a second stream of an emulsifier into said first stream, to form an emulsion in said first mixing chamber; and B. a second mixing chamber, adjacent to said first mixing chamber, including a third port for introducing a cross-linking solution, said cross-linking solution containing a predetermined amount of a cross-linking agent in a cross-linking solvent, into said second mixing chamber.

25. A method for producing drug-loaded microparticles, comprising the steps of: A. introducing a first stream, comprising an alginate and the drug, at a predetermined flow rate into a first mixing block to form alginate droplets containing the drug; B. introducing a second stream of an emulsifier at a predetermined flow rate into said first mixing block; C. forming an emulsion of said alginate droplets and said emulsifier in said first mixing block; and D. transporting said emulsion from said first mixing chamber and into a container that contains an amount of a cross-linking agent.

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File: DWPI

Nov 22, 1974

DERWENT-ACC-NO: 1975-04328W

DERWENT-WEEK: 197503

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TITLE: Multiple entry mixing chamber - for blending polymeric reagents or emulsion  
without using mechanical agitation

PRIORITY-DATA: 1973DE-2314459 (March 23, 1973)

## PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
FR 2222189 A	November 22, 1974		000	
DE 2314459 A	March 20, 1975		000	
GB 1401752 A	July 30, 1975		000	
JP 49128366 A	December 9, 1974		000	
JP 81041403 B	September 28, 1981		000	

INT-CL (IPC): B01F 5/04; B29B 1/06; B29B 5/04; B29D 27/02; F16K 11/02